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Role of risk stratification by SPECT, PET, and hybrid imaging in guiding management of stable patients with ischaemic heart disease: expert panel of the EANM cardiovascular committee and EACVI

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Risk stratification has become increasingly important in the management of patients with suspected or known ischaemic heart disease (IHD). Recent guidelines recommend that these patients have their care driven by risk assessment. The purpose of this position statement is to summarize current evidence on the value of cardiac single-photon emission computed tomography, positron emission tomography, and hybrid imaging in risk stratifying asymptomatic or symptomatic patients with suspected IHD, patients with stable disease, patients after coronary revascularization, heart failure patients, and specific patient population. In addition, this position statement evaluates the impact of imaging results on clinical decision-making and thereby its role in patient management. The document represents the opinion of the European Association of Nuclear Medicine (EANM) Cardiovascular Committee and of the European Association of Cardiovascular Imaging (EACVI) and intends to stimulate future research in this field.

Keywords risk stratification • SPECT • PET • hybrid imaging

Introduction

Risk stratification has become increasingly important in the management of patients with ischaemic heart disease (IHD). Recent guidelines recommend that patients with suspected or known IHD have their care driven by risk assessment.¹ The association between risk assessment and medical intervention is based on the concept that optimal improvement in outcome is achieved by linking high-risk

measures, obtained by the different imaging modalities, to risk-reducing therapies. In this era, new and existing technologies require a well-defined body of evidence on its benefit, to support resource utilization. Myocardial perfusion imaging (MPI) is the most widely used stress imaging procedure in the management of patients with IHD.² Gated single-photon emission computed tomography (SPECT) and positron emission tomography (PET) MPI provide important prognostic information on the extent and severity of

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myocardial perfusion abnormalities, including myocardial ischaemia. The results, obtained by SPECT and PET, specify the functional significance of the disease state and its relationship to event risk. On the other hand, hybrid cardiac imaging, either with SPECT or PET combined with coronary computed tomography angiography (CCTA), depicts cardiac and vascular anatomical abnormalities and their functional consequences in a single setting. This combination of techniques appears to offer superior information compared with either stand-alone or side-by-side interpretation of the data sets in patients with suspected or known IHD.³ The purpose of this position statement is to summarize current evidence on the value of cardiac SPECT, PET, and hybrid imaging in risk stratifying specific categories of patients with suspected or known IHD. In addition, it evaluates the impact of imaging results on clinical decision-making and thereby its role in patient management. The document represents the opinion of the European Association of Nuclear Medicine (EANM) Cardiovascular Committee and of the European Association of Cardiovascular Imaging (EACVI) and intends to stimulate future research in this field.

Patients with suspected IHD

Asymptomatic patients

Approximately half of acute coronary syndromes occur in patients who were asymptomatic until the day of their event, of which 48% have only one or even none of the traditional risk factors.⁴ This has prompted a demand for effective screening tools to reduce the high toll of unexpected coronary events by more individualized risk stratification. The use of imaging, in particular MPI, for the screening of asymptomatic but potentially hazardous IHD is a highly debated topic of preventive cardiology. Several expert consensus documents and international guidelines have given controversial recommendations.⁵ Those who are in favour of imaging-based screening agree upon its potential value in selected high-risk populations.⁶ However, until now conclusive evidence is lacking that detecting asymptomatic preclinical IHD by MPI with subsequent therapeutic intervention may reduce risk, beyond that indicated by risk factor profiling and traditional conservative risk reduction strategies. Thus, clinical risk assessment forms the basis for deciding on the intensity of additional screening with MPI, especially in selected high-risk population. Coronary artery calcium score (CACS) was proposed as a gatekeeper to identify asymptomatic subjects at risk for which further screening radionuclide MPI may be justified.⁷ Indeed, abnormal myocardial perfusion is rare below a CACS threshold of 100, but the prevalence of abnormal scans increases progressively with higher CACS. Notably, moderate-to-severe myocardial ischaemia was found in 8.6% of patients with CACS ≥ 1000 . Several prospective follow-up studies indicate that the use of CACS and radionuclide MPI has additional prognostic value (albeit mainly in symptomatic patients). In particular, an incremental prognostic value of CACS in 977 asymptomatic patients with normal MPI was reported.⁸ There was a 3.6-fold relative increase for any cardiac event and a 2.8-fold relative increase for death/myocardial infarction when the CACS was severe (>400) vs. minimal (≤ 10). Based on these data, the Appropriate Use Criteria consider screening with MPI appropriate in asymptomatic patients with a CACS >400 , or a

CACS between 100 and 400 and high IHD risk by traditional criteria.⁶ Silent myocardial ischaemia is also highly prevalent (27%) in asymptomatic male siblings of patients with onset of IHD before the age of 60 years and is independently associated with incident IHD (in two-thirds with an acute coronary syndrome) during the ensuing 10 years.⁹ Therefore, some investigators have suggested a tiered screening approach to subjects with a family history of premature IHD where a CACS could be used as gatekeeper of screening MPI.¹⁰ Non-invasive quantification of absolute myocardial blood flow by PET allows the detection of abnormal vasodilatory response to intravenous adenosine patients with a family history of CAD and high-risk lipid profiles. Early assessment of alterations of vascular reactivity to adenosine in relation to high-risk lipid profiles in asymptomatic patients may allow early detection of preclinical atherosclerosis and may initiate modification and/or elimination of risk factors.¹¹

Symptomatic patients

The prognostic value of MPI with SPECT in symptomatic patients with suspected IHD has been validated extensively. Pooled analyses from large observational databases comprising close to 40 000 patients unambiguously demonstrate that a normal MPI yields a favourable prognosis with an annualized event rate of 0.6%, which is similar to the general population.¹² Although the warranty period of a normal MPI interacts with the patient's risk profile, a low event rate has been reported for over a period as long as 7 years.¹³ Conversely, an abnormal scan confers a three- to seven-fold increase in annual cardiac events. The likelihood of events is related to the extent and severity of perfusion defects, fixed and/or reversible, and the associated prognostic risk needs to be interpreted in light of the baseline risk profile of the individual patient.¹⁴ Next to perfusion assessment, important additional prognostic information can be retrieved from the acquired SPECT, that is, left ventricular (LV) volumes and function (e.g. ejection fraction). A clear relationship between the extent of LV dysfunction and prognosis, independent from clinical baseline characteristics or perfusions defects, has been demonstrated. As well, evaluation of transient LV dilatation has been linked to extensive IHD due to post-stress LV dysfunction.¹⁵ Although risk stratification with SPECT imaging is important, improvement of prognosis through an imaging-guided approach is an obvious superior goal. Hachamovitch et al.¹⁶ have suggested that revascularization procedures might be beneficial to impact outcome only in the presence of ischaemia involving 10% or more of the LV myocardium. In a prospective nuclear sub-study of the COURAGE trial, this notion was underscored, whereby an ameliorated prognosis seemed to be related to the extent of ischaemia reduction as displayed with SPECT.¹⁷ These overwhelming data highlight that SPECT has powerful prognostic value but may additionally be used to guide patient management to influence outcome. In analogy to SPECT, PET holds strong prognostic information beyond traditional cardiovascular risk factors.¹⁸ In contrast to SPECT, PET offers the possibility to routinely quantify perfusion in absolute terms and calculate coronary flow reserve (CFR), which has incremental prognostic value over evaluation of perfusion defects alone. Murthy et al.¹⁸ demonstrated that a blunted CFR was one of the strongest prognostic factors and trumps clinical risk scores as well as relative perfusion abnormalities. Interestingly, apparent normal perfusion images with a homogenous

tracer distribution can be reclassified based on diffusely blunted hyperaemic myocardial blood flow (MBF) or CFR. Several studies have revealed that this subset of patients is at increased risk for future cardiac events.¹⁹

Combining CACS with MPI adds incremental prognostic value in patients with and without myocardial ischaemia, although ischaemia appears to be a more potent predictor of future cardiac events than coronary calcification.⁸ Improved risk stratification, by adding anatomical information of CCTA to functional data obtained with MPI, has also been documented. Pioneering studies documented the potential role of PET/CT technique to add functional information on the pathophysiological impact of a lesion, allowing accurate clinical decision-making on the best therapeutic strategy.²⁰ Interestingly, hybrid PET/CT allowed combination of angiography and perfusion imaging in short, quantitative, low-radiation-dose protocols.²¹ The likelihood of diagnosing obstructive IHD by invasive coronary angiography (ICA) is highest when patients have been screened with a hybrid imaging protocol, and both CCTA and MPI revealed abnormalities.²² Also the use of a sequential imaging approach provides particular additional value to risk stratify patients when either functional or anatomical evaluation displays ambiguous results.²³ On the other hand, annualized even rate of a normal MPI significantly increases when CCTA displays a coronary lesion of >50% (0.6 vs. 3.8%). The general consensus of the aforementioned studies is that hybrid assessment provides complementary rather than overlapping prognostic information. Such an approach can accurately position the patient within the various stages of atherosclerosis.³

Patients with known IHD

In patients with known IHD, atherosclerotic changes in the coronary arteries have to be taken for granted. Therefore, testing for ischaemia may add the most important information for further decision-making, especially, since secondary prevention should have already been initiated at the point of IHD diagnosis. Taking into account that IHD is a chronic progressive disease, re-evaluation of IHD risk may be beneficial. Serial testing using MPI is widely used in guiding patient care despite the lack of well-defined appropriate use criteria.² The first prospective assessment of appropriate use of MPS regarding its prognostic value in a patient population with known or suspected IHD demonstrated higher inappropriate use rates compared with previous reports, also demonstrating that the inappropriate use of MPI impaired its value for risk stratification.²⁴ Although this study has some important caveats, it demonstrated the necessity for more data, studying the variability in inappropriate rates and the prognostic value of appropriate use criteria in other specific patient populations.

Stable IHD

In the follow-up of patients with stable IHD, no randomized trials are available evaluating the impact on outcome of different strategies. Despite no data suggest that any form of routine stress testing or imaging improve outcome, repeat risk stratification may be considered after expiration of the 'warranty period' of an examination. Multiple clinical factors play an important role in patients with normal MPI, affecting their risk and altering the duration of a 'warranty period' for a normal perfusion scan.²⁵ A patient-tailored approach

based on clinical judgement has to be used to determine the benefits and risks of repeat risk stratification by cardiac imaging. Serial MPI provides valuable means to guide patient management and to study the impact of various interventions.² In particular, serial imaging may be useful in both clinical and research arenas to assess the value of novel anti-ischaemic therapies. The concerns of radiation exposure have been addressed by MPI technology innovation. The new-generation cadmium-zinc-telluride (CZT) gamma cameras, which allow acquisition of high-quality images using smaller doses of radio-tracer (Figure 1), have the potential for decrease patient radiation exposure also for hybrid imaging (Figure 2). That represents one of the main reached goals in using radionuclide MPI in guiding patient management. In patients with multi-vessel disease or complex IHD, the difficulties in identifying balanced flow reduction can be overcome with quantitative myocardial perfusion measures by PET. A better delineation of at-risk myocardium with quantitative CFR may also improve risk stratification in patients with known IHD. As underlined by the INSPIRE (Adenosine Sestamibi Post-Infarction Evaluation) study, MPI early after myocardial infarction was a safe and effective risk stratification strategy for identifying a large low-risk population that could be targeted for medical therapy and early hospital discharge.²⁶ Moreover, in patients with remote prior myocardial infarction, MPI added incremental value to pre-scan information and was highly predictive and cost-efficient in the risk stratification of these patients.²⁷ Patients with known IHD who underwent serial MPI imaging demonstrated that adding PCI to optimal medical therapy resulted in greater reduction in inducible ischaemia compared with optimal medical therapy alone. This benefit was most pronounced among patients with more severe baseline ischaemia (Figure 3). Finally, the magnitude of residual ischaemia on follow-up MPI was proportional to the risk for death or MI, and a 5% reduction in ischaemia was associated with a significant reduction in risk.¹⁶

Patients after revascularization

In symptomatic patients after PCI and coronary artery bypass grafting (CABG), MPI testing is appropriate²⁸ for diagnosis, risk stratification, and clinical decision-making. On the contrary, in asymptomatic patients after PCI and CABG, MPI rarely is appropriate, except in case of incomplete revascularization, or if performed >2 years after PCI or >5 years after CABG. The appropriateness of MPI in these patients is based on the incremental prognostic value of MPI after revascularization.²⁹ Evidence of silent ischaemia 6 months after PCI predicted a worse outcome and tended to have a better outcome than symptomatic ischaemia. Even 5 years after PCI, target-vessel events were more frequent than IHD progression assessed by remote events. However, remote events, often silent, accounted for up to 40% of all adverse events. This observation underscores the importance of IHD progression and of optimized secondary prevention strategies in addition to revascularization.²⁹ In selected CABG patients, hybrid imaging PET or MPI combined with CTCA may provide important information for further risk stratification.³⁰

Heart failure

Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood: either with a reduced (<50%) or preserved EF (≥50%). In

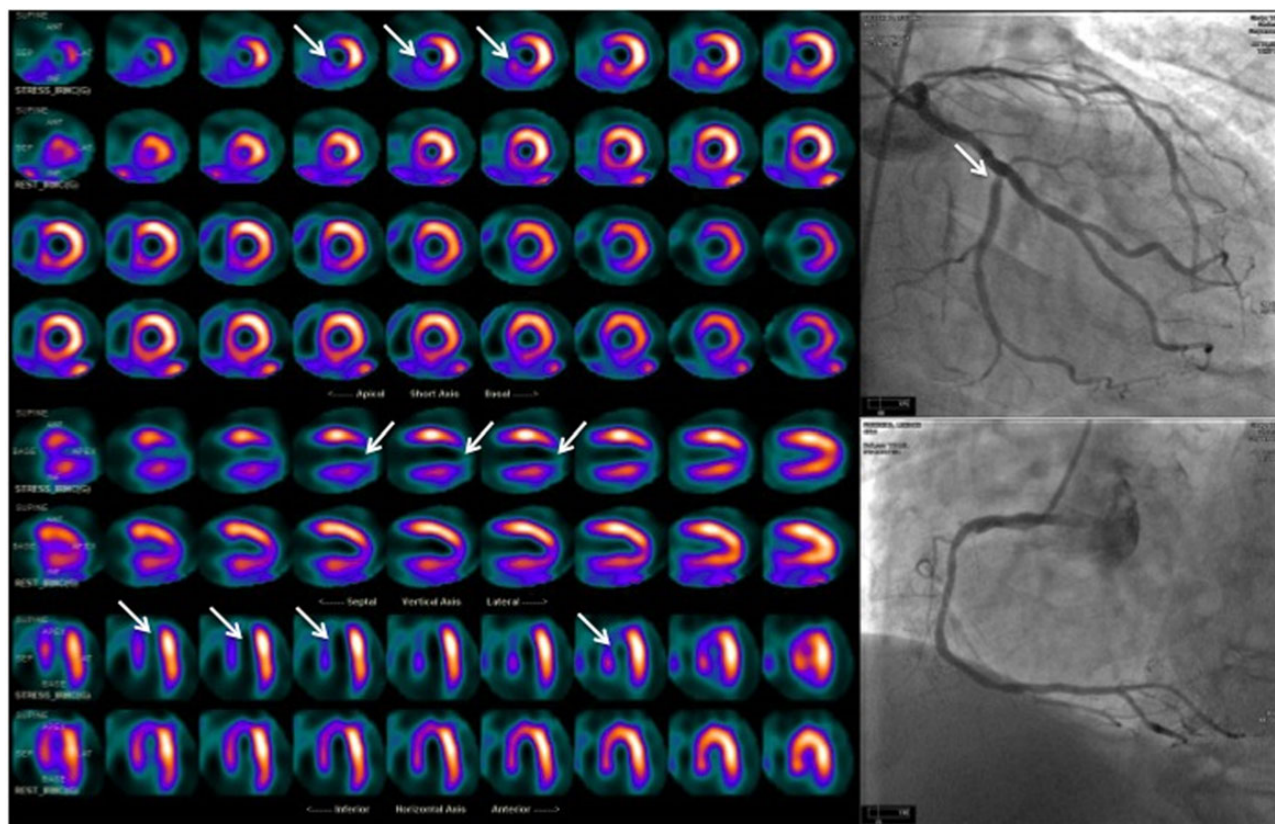


Figure 1 Case example. Dipyridamole-rest low-dose cadmium-zinc-telluride MPI (dosimetry 4.3 mSv). Asymptomatic male (55 years) with diabetes, normal resting function and negative stress test. MPI images showed perfusion defects (white arrows) of the distal anterior, anterior septum, and apical walls (LAD territory). An intermediate stenosis of the marginal branch of the left circumflex coronary artery (white arrows) does not correspond to any reduction of flow reserve. The main lesion was successfully treated by angioplasty.

addition to existing medical therapies for HF that have been successful in reducing mortality and extending survival, there has been a rapid increase in the use of implantable devices. All together these evolutions have an increasing impact on healthcare budgets. Therefore, better treatments for and earlier detection of HF are imperative. The dramatic deterioration in quality of life and prognosis when a patient progresses from asymptomatic LV dysfunction to overt HF suggests that only a programme of screening and prevention will effectively reduce the public health burden. Moreover, the economic consequences of developing overt HF suggest that such an approach is likely to be cost-effective. The 2013 American College of Cardiology Foundation (ACCF)/AHA guidelines on HF recommended that cardiac catheterization with coronary angiography is reasonable in patients with new onset HF of uncertain cause who would be eligible for revascularization.³¹ Non-invasive imaging to detect myocardial ischaemia and viability was considered reasonable in IHD patients with no angina and new onset HF, assuming that the patient is eligible for revascularization. The guidelines also noted that non-invasive imaging might be considered to define the likelihood of IHD in other patients with HF and LV dysfunction. This is in line with the 2012 ESC guidelines for the diagnosis and treatment of HF, that

give a IIA recommendation for considering MPI in HF patients thought to have IHD to determine extension of ischaemia and viability before revascularization. As a matter of fact, the appropriate patient selection for revascularization procedures is crucial and should be based on an accurate assessment of both possible risks and benefits. The assessment of myocardial viability has been an important prerequisite in the decision-making regarding revascularization as supported by a meta-analysis showing that after revascularization patients with myocardial viability had a better outcome compared with those without myocardial viability.³² However, after the STICH (Surgical Treatment for Ischemic Heart Failure) trial and especially the viability sub-study, questions have arisen regarding assessing viability testing in patients with LV systolic dysfunction and IHD before revascularization.³³ The STICH study reported no impact of viability on the primary end point of all-cause mortality in patients with ischaemic severe HF randomized to revascularization or optimal medical therapy. The STICH trial presented some limitations; the main methodological one was the definition of myocardial viability. A significant reduction in cardiac events in patients with LV dysfunction and suspected coronary disease for FDG PET-assisted management vs. standard care has been

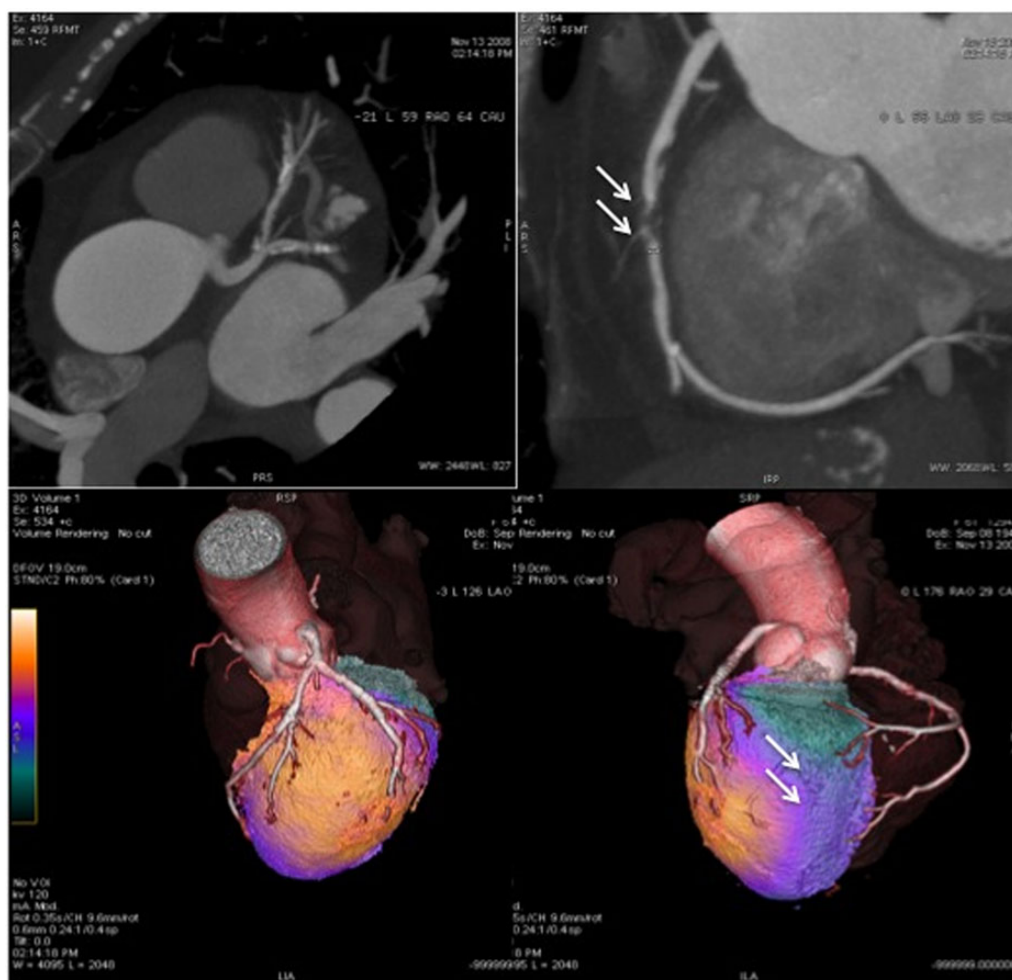


Figure 2 Case example. Hybrid images (MPI by CZT and CCTA, dosimetry 5.7 mSv). Female (65 years), several risk factors, previous percutaneous coronary revascularization procedure on left circumflex coronary artery and new onset of atypical angina. CCTA showed significant stenosis of right coronary artery, with reduction of flow after stress in the same territory documented by stress MPI (white arrows). The fusion images showed concordance between coronary anatomy and functional evaluation.

demonstrated.³⁴ Current HF guidelines recommended consideration of non-invasive imaging for the assessment of both inducible ischaemia and viable myocardium in the HF population. Early revascularization in the setting of significant hibernating myocardium was associated with improved survival compared with medical therapy, especially when the extent of viability exceeded 10% of the myocardium.³⁵

Myocardial ^{123}I -meta-iodobenzylguanidine (^{123}I -mIBG) scintigraphy reflects the cardiac sympathetic activity. Recently, ^{123}I -mIBG scintigraphy has been shown to be an independent predictor of ventricular arrhythmia, sudden cardiac death, and appropriate ICD discharges in HF patients with NYHA II-III and LV ejection fraction $\leq 35\%$.³⁶ However, ^{123}I -mIBG scintigraphy is not included in the current HF guidelines. This may be explained, in part, by the relative lack of large patient cohort trials. In addition, the role of cardiac innervation imaging techniques in identifying high-risk patients with

mild to moderate systolic dysfunction (EF $> 35\%$) has not been investigated yet.

Specific patient population

Women

Despite the recent decline in cardiovascular death rate in women, IHD is still the prevalent cause of mortality in women. Given the lower prevalence of obstructive IHD, greater variety of (atypical) symptoms, and commonly lower functional capacity, detection of IHD can be challenging in women despite there are no differences between women and men in the diagnostic evaluation. Recent data of 'What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN)' trial endorse the use of exercise tolerance test (ETT) with the possibility for follow-up evaluation with stress MPI for

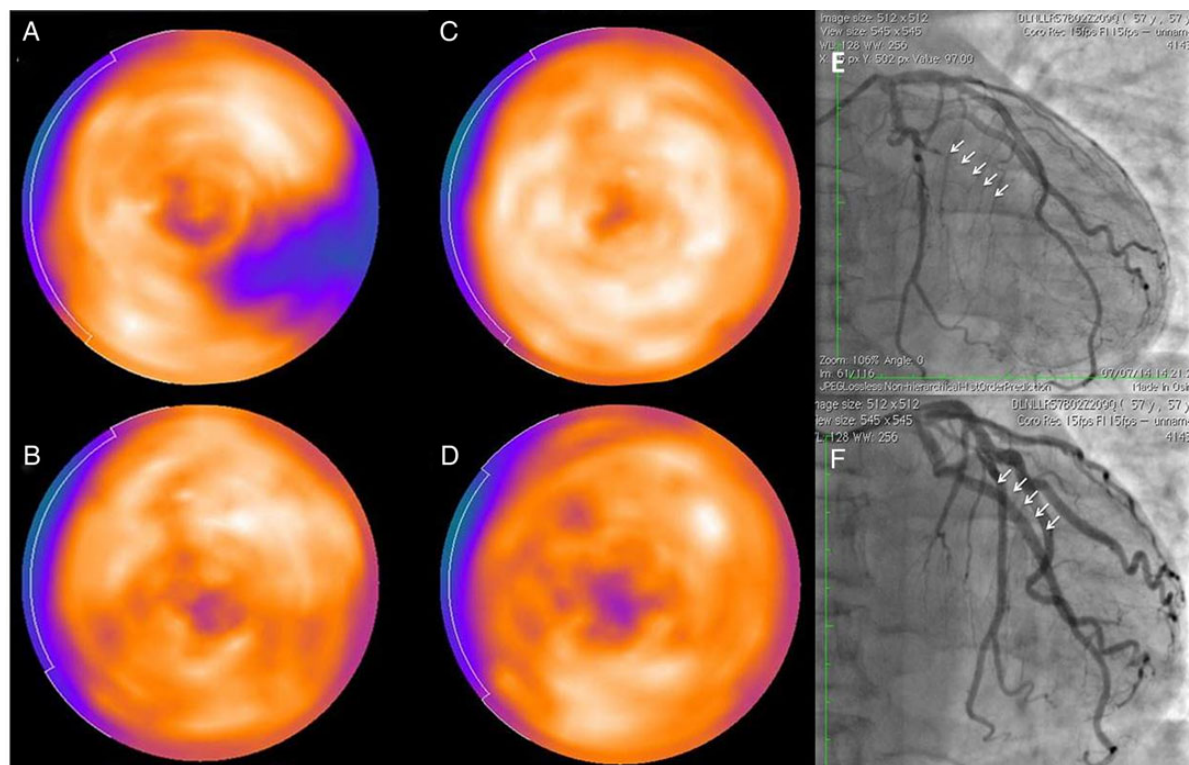


Figure 3 Case example. Coronary revascularization guided by severe myocardial ischaemia at rest-stress ^{82}Rb -PET. Baseline stress (A) and rest (B) myocardial perfusion imaging shows a severe myocardial ischaemia (>10%) completely resolved at stress (C) and rest (D) imaging after coronary revascularization procedure. In the pre-procedural coronary angiography (E), the white arrows show occluded II obtuse marginal branch of a dominant circumflex artery of the LCA. In post-percutaneous coronary intervention angiography (F), the white arrows indicate the treated II obtuse marginal branch with a good calibre and large extension towards the inferior and lateral wall of the left ventricle.

women with indeterminate or abnormal electrocardiographic and/or other ETT alterations. Such a strategy yielded comparable 2-year rates of major adverse IHD outcome.³⁷ In women with normal MPI, even in those women with high pre-test likelihood, the cardiac event rate is <1%.³⁶ Compared with a general cardiovascular risk population, the size and severity of the perfusion abnormality are also paralleled with an increase in cardiac event rate.³⁸ Perfusion imaging by PET or PET/CT has the same advantages as for male subjects over SPECT owing to improved spatial resolution, image quality, reduction in breast artefacts, lowered radiation exposure, and possibility to quantify MBF and CFR. Applying resting/stress ^{82}Rb -PET perfusion imaging, 5-year IHD mortality ranged from 0.9 to 13% for women with 0 to $\geq 15\%$ stress-induced myocardial perfusion defects.³⁹ Reductions in hyperaemic MBFs and CFR have been reported to carry important diagnostic and prognostic information in cardiovascular risk individuals with or without clinically manifest IHD. It has been demonstrated that coronary microvascular dysfunction identifies men and women at increased clinical risk.⁴⁰ In this scenario, PET flow studies have demonstrated that hormone replacement therapy with oestrogen alone or in concert with progesterone in post-menopausal women, in addition to standard preventive medical intervention of traditional cardiovascular risk factors, may contribute to preserve myocardial perfusion and the functional integrity of coronary circulatory function.⁴¹

Diabetic patients

Type 1 and type 2 diabetes mellitus (DM) is commonly paralleled by the early development of accelerated IHD that is held responsible for excess morbidity and mortality in these patients. Diabetic patients have a high risk for cardiovascular events and tend to have more often silent CAD than non-diabetic patients.⁴² It has been demonstrated that presence of perfusion abnormalities in diabetic patients confer a significantly worse prognosis, in particular in women and insulin-dependent individuals, than comparable perfusion abnormalities in patients without diabetes.⁴³ A normal MPI in diabetic patients is associated with a significantly better outcome than in those with perfusion abnormalities (annual cardiac death rate in non-insulin-dependent DM: 1.8 vs. 4.7%; and insulin-dependent DM: 2.5 vs. 9.0%). However, the prognosis of diabetic patients was still worse compared with non-diabetic patients. In the DIAD (Detection of Ischemia in Asymptomatic Diabetes) screening group, MPI was able to accurately risk stratify patients based on perfusion findings, with a higher event rates in patients with moderate or large perfusion defects compared with those with only mildly abnormal or normal MPI.⁴⁴ In this study, a low prevalence of patients with high-risk MPI abnormalities was observed, explaining probably why also screening did not show any difference on outcome compared with aggressive medical treatment. As a matter of fact, the 2009 ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM Appropriate Use Criteria for

Cardiac Radionuclide Imaging, consider screening with MPI appropriate in asymptomatic patients with high IHD risk or IHD risk equivalents such as diabetes.⁶ In asymptomatic diabetic patients, analytical approaches for stress MPS that establish the reclassification of events may serve for estimation of improved outcomes.⁴⁵ In particular, stress-induced ischaemia by gated MPI influences the temporal characteristic of the patient's risk at long-term follow-up. Thus, an MPS-adjusted strategy seems to be useful to refine risk estimate in asymptomatic diabetic subjects.⁴⁵ Recently, in high-risk asymptomatic patients with diabetes BARDOT (BASel high Risk Diabetic Outcome Trial) documented that patients with normal MPI (78%) have a low rate of first manifestations of IHD. Patients with abnormal MPI at baseline (22%) have a seven-fold higher rate of progression to 'overt or silent IHD,' despite therapy.⁴⁶ The American Diabetes Association's (ADA's) Standards of Care recommendation suggests that routine screening for IHD in asymptomatic diabetic patients is not recommended because it does not improve outcomes as long as IHD risk factors are treated.⁴⁷ As a matter of fact, the joint American Diabetes Association (ADA), European Society of Cardiology (ESC), and European Association for the Study of Diabetes (EASD) guidelines⁴⁸ recommend IHD screening in DM with MPI when there is evidence for atherosclerotic process or cardiac symptoms such as (i) abnormal resting ECG, (ii) evidence of peripheral or carotid occlusive arterial disease, and (iii) in DM patients with symptoms suspicious of IHD (i.e. chest pain, dyspnoea, fatigue). The role of cardiac PET for the assessment of myocardial perfusion and flow may be seen not only in the detection of more advanced stages of IHD in DM. In particular, PET might be pivotal in the identification and characterization of functional abnormalities of the coronary circulation, which have been regarded as functional precursors of the IHD process.¹⁹ Notably, among DM patients without IHD, those with impaired CFR have event rates similar to those of patients with known IHD. In contrast, DM patients with maintained CFR have event rates comparably low with those without known IHD or DM and a normal stress perfusion and systolic function.⁴⁹ More recently, glucose-lowering treatment has demonstrated that coronary endothelial function is independently associated with a slowed progression of coronary artery calcification in DM.⁵⁰ Whether PET-outcome-guided treatment, with the aim of improving hyperaemic MBF and/or CFR, will result in an improved patient outcome in DM remains to be seen.

Elderly

Over the last decades, there has been a steady increase in the prevalence of individuals older than 75 years. IHD is the most prevalent cause of morbidity and mortality in this age group, while rates have not fallen over time as they have been observed for younger individuals.⁵¹ In a retrospective MPI study in 5200 elderly patients with a follow-up of 2.8 ± 1.7 years, cardiac death rates significantly increased with increasing severity of abnormalities on MPI from normal, mildly abnormal, and moderately-to-severely abnormal myocardial perfusion with pharmacological stress (1.9 vs. 2.7 vs. 7.8%) or exercise stress (0.7 vs. 1.0 vs. 2.7%). As observed for SPECT, PET for myocardial perfusion may aid in selecting elderly patients at risk for cardiovascular events. However, it is important to be aware that resting MBF is commonly higher with increasing age related to an increase of baseline myocardial work, which again

leads to lower CFR values.⁵² Notably, above 70 years of age reported that hyperaemic MBFs appear to be lower. Apart from evidence of deficient neuroendocrine regulation of the cardiovascular system with advancing age, a diminished effect of exogenous applied adenosine on vascular smooth muscle cell relaxation of the coronary arteriolar vessels may account for the observed reduction in hyperaemic MBF in the elderly population.⁵² This again emphasizes the need to refine thresholds of hyperaemic MBFs and CFR, respectively, to differentiate normal and abnormal values for IHD in the elderly. Whether the assessment of CFR with PET may provide further incremental value in cardiovascular risk stratification over conventional perfusion imaging is an open question, needing further investigation.

Table 1 Key points for risk stratification in guiding management of

Asymptomatic patients

Screening with MPI in selected high-risk populations
CACS as gatekeeper of screening MPI for patients with higher risk coronary atherosclerosis and for low-risk patients with a family history of premature IHD or intermediate-risk patients

Symptomatic patients

MPI has powerful prognostic value (i.e. in the presence of ischaemia > 10% of myocardium) and may additionally be used to guide patient management to influence outcome
Additional prognostic information can be retrieved by function and volume parameters
Hybrid imaging demonstrated to improve risk stratification, by adding anatomical information to functional data
Hyperaemic myocardial blood flow (MBF) or CFR evaluation can reclassify patient with apparent normal perfusion images in guiding treatment

Patients with known IHD

MPI early after myocardial infarction is a risk stratification strategy for identifying a large low-risk population that could be targeted for medical therapy and early hospital discharge
Quantitative CFR, with a better delineation of at-risk myocardium, may improve risk stratification in patients with known IHD and in patients with multi-vessel disease
In selected CABG patients, hybrid imaging PET or MPI combined with CTCA may provide important information for further risk stratification

Heart Failure

MPI may be reasonable to detect myocardial ischaemia and viability in IHD patients with no angina and new onset HF eligible for revascularization
Cardiac Innervation imaging may be used as a predictor of ventricular arrhythmia, sudden cardiac death

Specific population

No differences between women and men in the diagnostic evaluation are found. Coronary microvascular dysfunction identifies both men and women at increased clinical risk
Screening of asymptomatic diabetic patients is not recommended
In high-risk asymptomatic diabetic patients MPI screening may be done to identify a higher risk patient subgroup

Table 2 Recommended future research with prospective clinical trials in

Asymptomatic patients

To reach a conclusive evidence that detecting asymptomatic preclinical IHD by MPI with subsequent therapeutic intervention, may reduce patients risk

To support that two-step risk stratification strategy (CACS and MPI) may determine a clinical benefit

Symptomatic patients

To demonstrate that reclassification by CFR in patients with apparent normal perfusion has a clinical impact to guide specific treatment

Patients with known IHD

The routine combination of anatomical information to functional data to risk stratify may become practical as hybrid SPECT-CT or PET-CT systems become more widely available

Heart failure

To define the clinical value of cardiac innervation imaging in HF patients, large patient cohort trials are needed

Specific population

To validate that high-risk asymptomatic diabetic patients with high-risk MPI imaging result improve their outcome after specific treatment

To demonstrate the role of potential coronary revascularization to reduce cardiac events in asymptomatic diabetic patients

Left bundle branch block patients

Complete left bundle branch block (LBBB) is associated with higher adverse outcomes including major cardiac events and mortality. In particular, LBBB occurs frequently in dilated cardiomyopathy and is associated with high cardiac morbidity and mortality.⁵³ LBBB induces inhomogeneous activation and deformation of the ventricles, leading to inefficient contraction. Experimental data suggest that the redistribution of local workload induced by LBBB provokes substantial changes in regional MBF and glucose metabolism, along with structural remodelling. Evaluation of MBF by PET should be useful to identify response to resynchronization therapy in dilated cardiomyopathy patients with LBBB. It has been demonstrated that LBBB induces relevant abnormalities in systolic deformation of the LV regions, leading to extensive redistribution of myocardial glucose metabolism and asymmetric LV hypertrophy.⁵⁴ Conversely, blood flows and MBF reserve were not influenced by contraction abnormalities and thereby were uniformly distributed across LV regions in patients with and without LBBB, indicating that these regional changes may further promote adverse LV remodelling leading to such extensive alterations not potentially reversible by resynchronization therapy.

Conclusions

This document provides a synopsis of available evidence on the prognostic value of SPECT, PET, and hybrid imaging in the evaluation of patients with suspected or known IHD. There is a substantial body of evidence on the prognostic role of these imaging modalities. However, in this era of prognostication, depth of evidence needs to be used to guide management of many important patient subsets. Some indications highlighted herein showed a significant role of imaging modalities in prognostication. Accordingly, k-points

of the panel are summarized in Table 1. In patients with suspected or known IHD, current evidence shows that extent and severity of myocardial ischaemia may be used to guide patient management to influence outcome. However, randomized studies are currently lacking. In addition, conclusive evidence is lacking that IHD assessment of asymptomatic patients by imaging modalities with subsequent therapeutic intervention may reduce risk beyond that indicated by risk factor profiling and traditional conservative risk reduction strategies. However, in selected high-risk asymptomatic IHD patients, additional screening with MPI can help in clinical risk assessment and form the basis for clinical decision-making. It remains to be addressed if non-invasive testing can reliably identify a considerable proportion of patients likely to benefit from an imaging-guided intervention in a cost-effective manner.

This expert panel encourages further research (Table 2) regarding the use of imaging for risk stratification by outcome trials to evaluate the clinical effects of imaging-based algorithms in guiding management of patients with suspected or known IHD. Moreover, it remains to demonstrate whether non-invasive testing can reliably identify a considerable proportion of patients likely to benefit from intervention in a cost-effective manner.

Conflict of interest: None declared.

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IMAGE FOCUS

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Bilateral arterial ducts with isolated left subclavian artery in ventriculo-arterial discordance, ventricular septal defect, and coarctation

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We report an unusual finding in a 5-day-old baby who had had an antenatal diagnosis of ventriculo-arterial (VA) discordance, ventricular septal defect (VSD), and great artery disproportion, suggesting postnatal development of Coarctation of the Aorta. Postnatal echocardiography confirmed VA discordance and VSD, but the arch anatomy was complex and less clear. There was additional sub-aortic stenosis, which had not been fully appreciated antenatally.

Cardiac magnetic resonance imaging (MRI) under general anaesthesia confirmed the right aortic arch but with a severely hypoplastic transverse arch and a dominant right ductal arch (see Supplementary data online, *Video S1*). A smaller left-sided arterial duct supplied the isolated left subclavian artery. The baby remained stable on a prostaglandin infusion and underwent total correction on Day 8 of life with an arterial switch operation with VSD closure, aortic arch reconstruction but with sacrifice of the left subclavian artery.

There have been previous descriptions of VA discordance with a right aortic arch and coarctation, including one patient with an isolated left subclavian artery, but in that case it was supplied retrogradely by a vertebral artery. This appears to be the first report of this particular constellation of bilateral ducts with an isolated left subclavian artery in VA discordance with a VSD and right-sided aortic arch with coarctation.

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Panel A: Anterior view showing disconnected left subclavian supplied by left arterial duct; *Panel B:* Right lateral view showing severely hypoplastic aortic arch and large right-sided ductal arch; *Panel C:* Left lateral view showing disconnected left subclavian and coarctation.

Supplementary data are available at *European Heart Journal – Cardiovascular Imaging* online.

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